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Transcatheter Treatment of Atrial Septal Aneurysm Associated With Patent Foramen Ovale for Prevention of Recurrent Paradoxical Embolism in High-Risk Patients

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OBJECTIVES This study sought to investigate the safety and efficacy of transcatheter treatment of atrial septal aneurysm (ASA) associated with patent foramen ovale (PFO).

BACKGROUND Patients with both ASA and PFO are at high risk for recurrent paradoxical embolism.

METHODS The procedural, echocardiographic, and clinical outcomes of 141 patients with ASA + PFO and ≥1 paradoxical embolic event undergoing transcatheter treatment were compared with 220 patients with PFO alone.

RESULTS Device success (ASA + PFO, 99.3%; PFO alone, 99.5%; $p = 0.75$) and procedural complications (ASA + PFO, 0.7%; PFO alone, 3.2%; $p = 0.12$) were similar in both groups. Maximal atrial septal excursion in patients with ASA + PFO decreased from 16 ± 4 mm before to 4 ± 3 mm after the intervention ($p < 0.0001$). At 6 months follow-up, right-to-left shunt was abolished in 120 (86%) patients with ASA + PFO, compared to 187 (85%) patients with PFO alone ($p = 0.80$). Freedom from recurrent transient ischemic attack, stroke, and peripheral embolism at 4 years was 95% (ASA + PFO) and 94% (PFO alone, $p = 0.70$), respectively. A residual right-to-left shunt after the intervention was the only predictor for recurrence (hazard ratio [HR] 6.9; 95% confidence interval [CI] 1.3 to 36.9, $p < 0.03$) in patients with ASA + PFO.

CONCLUSIONS Transcatheter treatment of ASA + PFO is safe and effective in patients with paradoxical embolism. The procedure effectively abolishes right-to-left shunt and decreases atrial septal mobility. Long-term prevention of recurrent events appears favorable when compared to patients with PFO alone. (J Am Coll Cardiol 2005;45:377–80) © 2005 by the American College of Cardiology Foundation

The prevalence of atrial septal aneurysm (ASA) in the general population ranges from 1% in autopsy (1) to 2.2% in transesophageal echocardiographic (TEE) series (2,3). Atrial septal aneurysm is rarely an isolated abnormality, but it is frequently (50% to 89%) associated with a patent foramen ovale (PFO) (1,2). Atrial septal aneurysm has been associated with cerebral ischemia (2,4), and patients with both ASA and PFO constitute a high-risk population with a three- to five-fold increased risk for recurrent events compared to patients with PFO alone (5). Although transcatheter closure of PFO alone (6–8) has been shown to be feasible, treatment of patients with ASA + PFO has not been systematically studied. We therefore investigated the safety and efficacy of transcatheter treatment of ASA + PFO in a cohort of consecutive patients with presumed paradoxical embolism and compared it to that of patients with PFO alone.

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METHODS

Patient population. One hundred forty-one consecutive patients with ASA + PFO and one or more documented ischemic stroke, transient ischemic attack (TIA), or peripheral embolism related to paradoxical embolism were recruited from two institutions: University Hospital, Bern, Switzerland, and Cardiovascular Center, Frankfurt, Germany. The control group consisted of 220 consecutive patients with PFO alone undergoing percutaneous PFO closure during the same period at the University Hospital, Bern, Switzerland. The study protocol was approved by the local Ethics Committees, and patients gave written informed consent. An embolic event was considered due to paradoxical embolism when the following criteria were fulfilled: 1) presence of PFO with or without ASA with spontaneous or inducible interatrial right-to-left shunt during contrast TEE, 2) clinically and/or radiologically confirmed ischemic stroke, TIA, or peripheral embolism, and 3) exclusion of any other identifiable cardiac, aortic, or cerebrovascular cause.

Echocardiography. At baseline before closure and six months after transcatheter treatment, a paired-contrast TEE study was performed. The diagnosis of ASA was made

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Abbreviations and Acronyms

ASA = atrial septal aneurysm
CI = confidence interval
HR = hazard ratio
PFO = patent foramen ovale
TEE = transesophageal echocardiography
TIA = transient ischemic attack

if: 1) the diameter of the base of the aneurysm measured ≥15 mm, and 2) the excursion of the aneurysmal membrane exceeded ≥10 mm (3). Spontaneous or provoked right-to-left shunt was graded according to the amount of bubbles crossing the interatrial septum: grade 0 = none, grade 1 = minimal (1 to 5 bubbles), grade 2 = moderate (6 to 20 bubbles), and grade 3 = severe (>20 bubbles) (6).

Follow-up evaluation. Outcome after the intervention was prospectively assessed for up to six years. Two patients with ASA + PFO and five patients with PFO alone were lost to follow-up because of emigration. Patients underwent a structured telephone interview, addressing recurrent events, device problems, and health status at regular intervals. Recurrent ischemic stroke, TIA, or peripheral embolism were considered end points. Patients with suspected recurrent events were re-examined by a neurologist, and an imaging study of the brain was repeated.

Statistical analysis. Continuous variables are expressed as mean ± 1 SD and were compared by a two-sided *t* test. Categorical variables are reported as counts and percentages, and were compared by chi-square analysis. Estimates for freedom from recurrent TIA, stroke, and the composite of TIA, stroke, or peripheral embolism were obtained using the Kaplan-Meier method. The log-rank test was used for univariate analysis of independent predictors of recurrence. Hazard ratios (HRs) and 95% confidence intervals (CIs) for each independent variable were obtained by proportional hazard regression analysis. Statistical significance was assumed with a p value <0.05.

RESULTS

Procedural outcome. Demographic data are summarized in Tables 1 and 2. A total of seven different atrial septal occlusion devices were utilized depending on institutional preference and device availability (Table 3). Device success was 99.3% in patients with ASA + PFO and 99.5% in patients with PFO alone (p = 0.75). Procedural complications occurred with similar frequency in patients with ASA + PFO (one device embolization: 0.7%) and patients with PFO alone (four device embolizations, one cardiac tamponade, and two vascular access site complications: 3.2%; p = 0.12).

Table 1. Demographics

	ASA + PFO	PFO Alone	p
Patients (n)	141	220	
Age (yrs)	49 ± 13	50 ± 13	0.73
Male gender	75 (53%)	119 (54%)	0.86
Follow-up (yrs)	2.5 ± 1.6	2.3 ± 1.8	0.25
Index event			0.43
Ischemic stroke	83 (59%)	138 (63%)	
Transient ischemic attack	48 (34%)	73 (33%)	
Peripheral embolism	10 (7%)	9 (4%)	
Prior embolic events			
Mean number of events	1.7 ± 1.04	1.7 ± 1.07	0.89
More than one event	55 (39%)	83 (38%)	0.81

ASA = atrial septal aneurysm; PFO = patent foramen ovale.

Table 2. Right-to-Left Shunt as Assessed by Contrast Transesophageal Echocardiography

	ASA + PFO	PFO Alone	p
Shunt at baseline			0.18
Grade I	2 (1%)	7 (3%)	
Grade II	21 (15%)	46 (21%)	
Grade III	118 (84%)	167 (76%)	
Shunt six months after transcatheter treatment			0.80
No shunt	120 (86%)	187 (85%)	
Grade I	11 (8%)	19 (9%)	
Grade II	6 (4%)	6 (3%)	
Grade III	3 (2%)	7 (3%)	

Abbreviations as in Table 1.

Echocardiographic findings. The effect of transcatheter treatment of ASA + PFO on atrial septal mobility and right-to-left shunt is summarized in Figure 1 and Table 2. Maximal atrial septal excursion of ASA decreased from 16 ± 5 mm before to 4 ± 3 mm after the intervention (p < 0.0001). A right-to-left shunt via the associated PFO was abolished in 120 (86%) patients, whereas a minimal, moderate, or large residual shunt persisted in 11 (8%), 6 (4%), and 3 (2%) patients, respectively. In patients with PFO alone, complete closure was achieved in 187 (85%) patients, whereas a minimal, moderate, or large residual shunt persisted in 19 (9%), 6 (3%), and 7 (3%) patients, respectively (p = 0.80 for the comparison with patients with ASA + PFO). Device size categorized as small (<30 mm; n = 83 patients) or large (≥30 mm; n = 58 patients) had no impact on the incidence of procedural complications (small 1.2% vs. large 0%; p = 0.40) and residual shunt rate (small 15% vs. large 14%; p = 0.89) in patients with ASA + PFO.

Clinical outcome. During follow-up, there were no differences with respect to recurrent TIA, stroke, and the composite of recurrent TIA, stroke, or peripheral embolism between patients with ASA + PFO and those with PFO alone (Table 4). Freedom from the composite end point of recurrent TIA, stroke, or peripheral embolism at four years was 95% and 94%, respectively (p = 0.70) (Fig. 2). The presence of a residual right-to-left shunt after transcatheter treatment of ASA + PFO was the only predictor for recurrent events (HR 6.9; 95% CI 1.3 to 36.9, p < 0.03) (Fig. 3).

DISCUSSION

Previous reports (6–8) have shown transcatheter treatment of patients with cryptogenic stroke and PFO alone to be

Table 3. Implanted Devices

Device Type	Patients (n)	Procedural Complications	Residual Shunt	Recurrent Embolism	Cumulative Follow-Up (Patient-Yrs)
ASA + PFO					
Sideris buttoned device	8	0	4 (50%)	0	52
Angel-wings occluder	5	0	1 (20%)	1	22
Amplatzer atrial septal occluder	4	1	1 (25%)	1	10
CardioSEAL/STARFlex septal occluder	13	0	2 (15%)	0	46
PFO-STAR septal occluder	36	0	6 (17%)	3	93
Amplatzer PFO occluder	56	0	5 (9%)	1	91
Helex septal occluder	19	0	1 (5%)	0	32
Totals	141	1 (0.7%)	20 (14%)	6	346
PFO alone					
Sideris buttoned device	24	4	10 (42%)	2	123
Angel-wings occluder	8	0	1 (13%)	1	35
Amplatzer atrial septal occluder	5	0	2 (40%)	0	26
CardioSEAL/STARFlex septal occluder	5	0	0	0	19
PFO-STAR septal occluder	46	3	8 (17%)	6	109
Amplatzer PFO occluder	131	0	11 (8%)	1	181
Helex septal occluder	1	0	0	0	1
Totals	220	7 (3.2%)	32 (15%)	10	494

Abbreviations as in Table 1.

feasible using a variety of trans-septal occlusion devices. Although most series included only a few patients with an associated ASA, the present study is the first series to investigate the safety and long-term efficacy of transcatheter treatment of ASA + PFO in a sizeable cohort of patients. The principal findings of the study are: 1) transcatheter treatment of ASA + PFO is safe; 2) procedural success and complications of transcatheter treatment of ASA + PFO are similar to the treatment of patients with PFO alone; 3) the additional presence of ASA does not adversely affect elimination of right-to-left shunt compared with PFO alone; and 4) the long-term risk of recurrent events after transcatheter treatment of ASA + PFO is comparable to that of patients with PFO alone.

Patients with ASA + PFO are at higher risk for stroke and stroke recurrence compared to patients with PFO alone, and secondary prevention with acetylsalicylic acid appears insufficient to protect against recurrence (4). Atrial septal aneurysm may act as facilitator for paradoxical embolism via the following mechanisms: 1) it may increase the PFO diameter due to the highly mobile atrial septal tissue, leading to a more frequent and wider opening of an otherwise small channel (9,10); 2) atrial septal aneurysm may promote right-to-left shunting by redirecting flow from the inferior vena cava toward the PFO (11); and 3) atrial septal aneurysm has been considered a nidus for local thrombus formation with subsequent embolization (1).

The results of the present study indicate that the right-to-left shunt as principal mechanism of ASA-related embolism can be effectively eliminated in the majority of patients. Transcatheter treatment of ASA + PFO also reduces atrial septal mobility. This effect most likely results from immobilization of redundant atrial septal tissue between the device discs. Initially, it was surmised that this

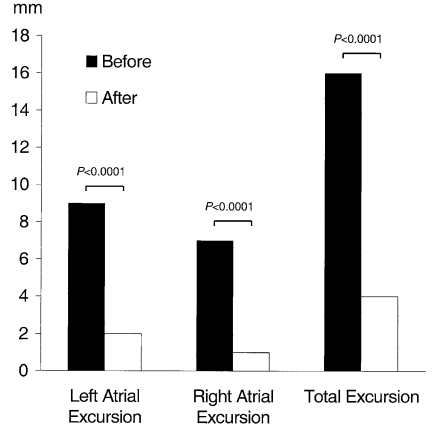

Figure 1. Effect of transcatheter treatment of atrial septal aneurysm and patent foramen ovale on atrial septal mobility as assessed by paired transesophageal echocardiography.

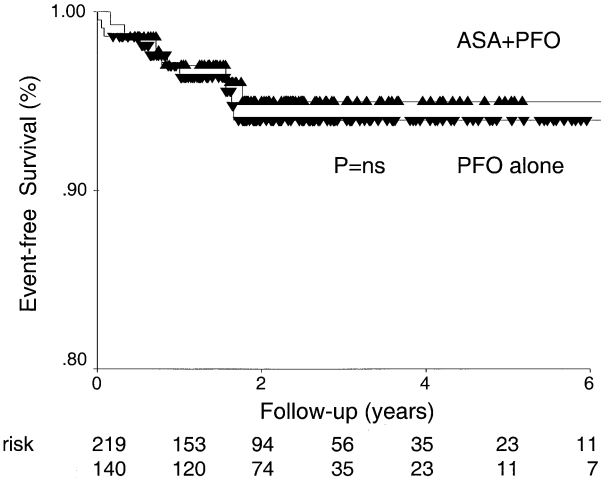

Figure 2. Freedom from the composite of recurrent transient ischemic attack, stroke, or peripheral embolism after transcatheter treatment for patients with atrial septal aneurysm and patent foramen ovale (ASA + PFO) and patients with PFO alone.

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Table 4. Recurrent Events

	Events		Probability of Event at Four Years*		Hazard Ratio (95% CI)†	p Value‡
	ASA + PFO	PFO Alone	ASA + PFO	PFO Alone		
Patients (n)	141	220				
Recurrent TIA, stroke, or peripheral embolism	6	10	5.0%	6.1%	0.82 (0.30–2.26)	0.70
Recurrent stroke	1	4	0.7%	2.6%	0.35 (0.04–3.11)	0.32
Recurrent TIA	5	4	4.3%	2.2%	1.72 (0.46–6.41)	0.41

*Probabilities of events were derived from Kaplan-Meier analyses. †Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from Cox regression analyses. ‡p values were calculated with the log-rank test.
TIA = transient ischemic attack; other abbreviations as in Table 1.

might decrease the potential for local thrombus formation. However, the current data refute this and corroborate that the PFO is instrumental, whereas the ASA acts as facilitator only. The present study also suggests that there may be no need to oversize devices in an attempt to stent the floppy septum. This observation could allow for the implantation of smaller devices more snuggly nested in the fossa ovalis, and thus more likely to afford complete closure of the PFO.

Study limitations. The following limitations should be considered in the interpretation of our results. 1) The diagnosis of paradoxical embolism remains presumptive, and cryptogenic embolism is not necessarily synonymous with paradoxical embolism. 2) The dimensional definitions of ASA vary, with excursions ranging from 6 to 15 mm. The aneurysmal excursion exceeded 10 mm in all patients in our study, and therefore, the results should apply to the majority of patients with ASA + PFO. 3) Comparison of patients with ASA + PFO from two centers with a control group from only one center increases the possibility of bias or confounders despite similar patient characteristics. 4) Patients with PFO alone have been included in the present study as a reference group to provide a comparison with respect to procedural, echocardiographic, and clinical outcome. However, this comparison is not randomized, and potential differences between patient groups beyond the interatrial septal abnormality cannot be excluded and may have affected the outcome.

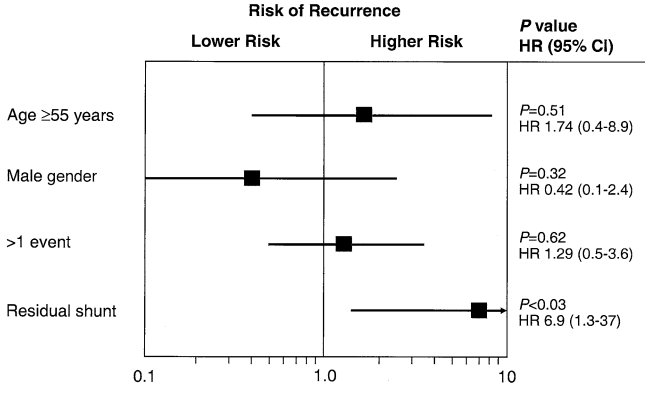

Figure 3. Predictors for the composite of recurrent transient ischemic attack, stroke, or peripheral embolism after transcatheter treatment of atrial septal aneurysm and patent foramen ovale. CI = confidence interval; HR = hazard ratio.

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